STATUS OF CLAIMS

Claims 5-7, 9, 11-26, 29 and 54-64 are all of the claims remaining in this application, all other claims having been voluntarily cancelled during prosecution of this application, Applicants reserving the rights to file continuation application son the subject matter of those cancelled claims and other subject disclosed but not claimed in this Application.

Claim 26 has been objected to as depending from a cancelled claim.

Claims 5, 6, 13, 14, 17, 18, 20, 21, 25, 26, 54, 55, 57 and 58 have been rejected under 35 USC 102(b) as anticipated by US Patent No. 5,869,463 (Major).

Claims 7, 9, 11, 15, 16, 19, 22, 29, 56 and 58 have been rejected under 35 USC 103(a) as unpatenable over Major (as applied against claim 5) when further considered with US Patent No. 5,497,770 (Morcos).

RECEIVED
CENTRAL FAX CENTER
FEB 2 6 2007

ARGUMENT AGAINST REJECTIONS

Claims 5, 6, 13, 14, 17, 18, 20, 21, 25, 26, 54, 55, 57 and 58 have been rejected under 35 USC 102(b) as anticipated by US Patent No. 5,869,463 (Major).

Claim 5 will first be discussed to emphasize specific limitations (not to the exclusion of other limitations or claim) that are particularly material to differentiation from this combination of references. Claim 5 recites:

> A **method for indicating viability of transplanted progenitor or stem cells** grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:
>
> non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture cells have been transplanted;
>
> **sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells** grown in a culture; and
>
> **using data from sensing said property** within said region **to indicate cell viability** from a transplant of progenitor or stem cells grown in a culture within the region **wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population.** (Emphasis added).

Errors by the Examiner Regarding the Factual Content of the Major et al. reference

It is asserted that Major et al. disclose a method for indicating viability of transplanted progenitor or stem cells grown in a culture (The Examiner citing col. 5, lines 31-67, col. 6, lines 1-16, col. 7, lines 33-41) which involves sensing a property indicative of cell viability using a medical device (col. 11, lines 28-36). This assertion does not

reflect the actual content of the Major et al. disclosure. Unlike the present application, Major et al. do not disclose the use of a medical device that supports sensing the viability of the cells while the cells are implanted in a human.

Major et al. actually describe the use of a number of *in vitro* (**not *in vivo***) methods to develop viable implantable cells. Monitoring of cell viability is performed before the cells are actually transplanted into human tissue and a patient is examined after implantation for only tumor formation. Claim 1 of Major, for example, discloses a method:

> "...comprising implanting into said mammal a therapeutically effective amount of a nontumorigenic and non-inflammatory immortalized human neuro-glial cell line..."

Figs. 1-2 of Major et al. similarly describe ex vivo preparation of implantable cells before they are implanted into tissue. Both Claim 1 and Figs. 1-2 of Major et al. disclose methods for monitoring cell viability before any transplant of the cells into a human. Figs. 3-8 and Fig.10 describe methods for post-mortem analysis of cell viability (histological examination of cell implants). Fig. 9 describes the use of MRI to evaluate the transplanted cells at a single time point 6 months after implantation, but only for tumor formation, not for cell viability.

None of the examples cited in Major et al disclose in vivo methods for monitoring or sensing cell viability following transplant of the cells into a human.

Examples 1, 6 & 7 describe in vitro methods for preparing the cells for implantation.

Example 2 describes surgical methods for implanting the cells, but not for monitoring cell viability in vivo.

Example 3 describes how "successful engraftment" of the cells was monitored by post-mortem histological methods, not by the recited steps of Claim 5:

> "...sensing a property within said region of a patient that is indicative of cell viability or inviability of transplanted progenitor or stem cells grown in a culture; and using data from sensing said property within said region to indicate cell viability from a transplant of progenitor or stem cells grown in a culture within the region wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population."

Example 4 describes how MRI was used 1 month following cell implant, but only tumor formation, not cell viability, was evaluated.

Example 5 describes only post mortem histological methods to evaluate the cell implant, which also is no sensing a property within a region of a patient indicative of cell viability. By its very nature, post mortem analysis cannot be within a region of a patient as there is no longer a patient, but a cadaver.

Thus, there is no teaching in Major et al. (as has been asserted) for using a medical device for *in vivo* monitoring of the viability of implanted cells. Although Major et al. describe the use of MRI to **initially position the cells at target locations in human tissues**, they do not provide any *in vivo* imaging method that enables the longitudinal monitoring of the survival of implanted cells over time. Major et al. simply state that

> "Persons of skill will understand how to determine proper cell dosages."

This is no more than a pretreatment or concurrent treatment consideration of initial dosage application of cells. It in no way senses cell viability. Additionally, this statement ignores recent published studies that poor implant survival is a key limitation to establishing transplant efficacy. Recent reports indicate that 80-95% of embryonic stem cells die within 48 hours after implantation. Moreover, surviving implanted cells may re-innervate only 25% of the host brain tissue and only at 25% of

normal density. Published studies of embryonic stem cell implants have shown a 10- to 100-fold variability in cell survival and in graft volume. Pathophysiologic changes at the implant site that compromise cell survival, such as reduced blood flow, increased tissue pH, and abnormal tissue concentrations of ions and neurotransmitters can be monitored **using the MR imaging and spectroscopy methods disclosed by the applicants**, but which are not even addressed in the Major et al. patent. Real time MR imaging at higher Tesla fields, such as disclosed by the applicants, can provide images identifying concentration changes of these introduced and production-stimulated materials, particularly by using RF microcoils in the region where the therapeutic agents are delivered.

It is also well established in the medical literature that stem cells have a propensity to migrate from the site of implant to remote locations. It is also known that stem cell migration is influence by trophic factors and pathophysiologic changes, such as ischemia. Thus, it is important that the present application provides an *in vivo* dynamic imaging method that can monitor cell migration and eventual in situ localization of implanted stem cells. By comparison, Major et al. disclose only post-mortem histological methods to evaluate cell migration and integration.

The presently claimed technology may be further distinguished from the teachings provided by Major et al. on the basis that certain claims expressly provide for a quantitative assessment of various parameters related to cell viability, as follows:

> "...an imaging means for quantitating the number of cells implanted into a tissue in a human body."
>
> "...an imaging means for quantitating the number of living cells implanted into a tissue in a human body."
>
> "...an MR imaging means for quantitating the number of cell-to-cell membrane contacts in a cell implant in a tissue in a human body."

"...an MR imaging method for quantitatively determining the apparent diffusion coefficient in a population of living cells implanted into a tissue in a human body."

"...an MR method for quantitatively determining the pH and fluid-electrolyte parameters in a population of living cells implanted into a tissue in a human body."

"...an MR method for quantitatively determining the phosphorus and water proton metabolites in a population of living cells implanted into a tissue in a human body."

...an MR imaging means for quantitating the functional capillary density of the tissue region contiguous with the cell implant.

None of these recitations recited in the claims are taught or even considered by Major et al., alone or in combination with secondary references.

Major et al. do not disclose an imaging means for quantitatively assessing physiologic and metabolic parameters of progenitor or stem cell implants that can non-invasively determine cell viability. The teachings of Major et al. relate to prospective planning of cell implants, as opposed to the claimed technology of a unique methodology of monitoring current operational events and past operational results. Major et al are thus looking at a different time frame than Applicants' claimed technology and are performing different tasks.

The presently claimed technology in this application in particular discloses methods to monitor non-invasively the ongoing viability of the cell implant in terms of whether the cells are adequately perfused by the local microvasculature. The present invention also discloses a method for quantitating the functional capillary density in the anatomic region of the cell implant, for quantitatively determining the metabolic status of a population of living cells implanted into a tissue, and for the MR-assisted visualization of molecular level changes in composition of the cell implant.

Independent Basis of Patentability Because of Quantitating of Cell Viability

Additionally, as recited in certain others of these claims **(Claims 54-58)**, neither the Lemelson or Palti references disclose how metabolic changes in implanted progenitor or stem cells can be quantitatively measured by non-invasive *in vivo* proton spectroscopy with local or volume RF-coils to obtain quantitative proton observable metabolites such as GABA, PCr, creatine, choline, and lactate. The quantitative feature of the present application is important because concentrations of lactate above 2-6 millimolar indicate a significant occurrence of dying or dead cells. Thus, unlike Lemelson and Palti, the present application describes how viable cell implants can be distinguished from dead or dying cells based on quantitative regional indications of lactate to metabolite levels.

The present application also discloses how non-invasive imaging technologies can track, in vivo, C-13 labeled glucose introduced directly into brain tissues together with the cell implant. Glucose metabolism in the cell implant is assessed by observing the resulting quantitative data from in vivo conversion of the C-13 labeled glucose into C-13 labeled metabolic by-products. The levels and turnover rates of glucose utilization, as measured by the concentrations of the converted compounds, reflect the ongoing viability of the cell implant. Thus, the methods disclosed by the applicants can be distinguished from the Palti patent in which glucose sensitive cells are implanted into tissue to function as surrogate 'glucodetectors' in patients with insulin-dependent diabetes.

Claims 7, 9, 11, 15, 16, 19, 22, 29, 56 and 58 have been rejected under 35 USC 103(a) as unpatenable over Major (as applied against claim 5) when further considered with US Patent No. 5,497,770 (Morcos).

The addition of Morcos to Major et al. does not overcome the deficiencies of Major et al. and in fact provides further distinctions and benefits in the system of the present invention. Although Morcos is attempting to verify cell viability, it is necessary

in his procedure to use a **highly invasive** technique which by its very nature may further damage cells. Morcos describes the use of a catheter to "provoke" cells and cause some specific activity which can then be observed or measured as with infrared observation or direct (through the catheter) measurement of ionic effects.

The clear and significant benefits of the present technology can be readily seen. Rather than penetrating the body into the tissue area and provoking tissue, the present system is capable of non-invasive imaging or the use of external imaging using only field coils to provide magnetic field activity (which would not provoke tissue). Morcos uses direct and internal measurement of parameters with a device that must be present in the immediate vicinity of the tissue and must itself create some provocation of the tissue to engender change that can then be observed by internal instrumentality. Coils, even if used in the claimed technology, do not themselves sense or observe, but merely generate a non-provocative field within which MR observation by the external system can be provided with greater resolution and image strength.

The non-tissue affecting benefits of the present system as compared to that of Morcos should be apparent. There is no motivation to in any way combine the systems of Major et al. and Morcos to provide a system or method such as that described in the claims.

A typical process for Morcos is described as:

> "Once the probe is positioned on the tissue of interest, a baseline measurement is taken. A substrate compound is infused into the tissue as additional measurements are taken. In many instances, it is advantageous to infuse a second substance, a trigger compound, while continuing to take measurements."

As can be seen, this is a highly invasive process wherein materials and apparatus must be locally introduced and local observation performed to provide any evidence of cell viability.

The rejection under 35 USC 103(a) is clearly in error and must be withdrawn.

RECEIVED
CENTRAL FAX CENTER

FEB 2 6 2007

CONCLUSION

All rejections have been traversed and overcome by these arguments.

All rejections of record have been shown in detail to be in error. The rejection should be reversed and all claims should be indicated as allowable.

Applicants believe the claims are in condition for allowance and request reconsideration of the application and allowance of the claims. The Examiner is invited to telephone the below-signed attorney at 952-832-9090 to discuss any questions that may remain with respect to the present application.

Respectfully submitted,
MICHAEL MOSELEY et al.

By their Representatives,
MARK A. LITMAN & ASSOCIATES, P.A.
York Business Center, Suite 205
3209 West 76th Street
Edina, MN 55435
(952)832.9090

Date 26 FEBRUARY 2007 By _____
Mark A. Litman
Reg. No. 26,390

I hereby certify that this correspondence is being sent by facsimile to the US Patent and Trademark Office addressed to Box: AMENDMENT, P.O. BOX 1450; Commissioner for Patents, Alexandria, VA 22313-1450 on 26 FEBRUARY 2007.

Name: Mark A. Litman

Signature